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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/355,014	09/13/1999	VANESSA HSEI	P1085R3	5890

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EXAMINER	
HELMS, LARRY RONALD 14	
ART UNIT	PAPER NUMBER

1642

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/355,014

Applicant(s)

HSEI ET AL.

Examiner

Larry R. Helms

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) 35-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-52 are pending.

Claim 14 has been amended.

Claims 1-34 are under examination.

2. Claims 35-52 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made without traverse in Paper No. 7.

Priority

3. The response acknowledges the priority date granted to the application for claims 1-34 of 1/22/98.

Rejections Withdrawn

4. The rejection of claims 1-17 and 32-33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims and arguments.
5. The rejection of claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilchek et al (Methods in Enzymology 104 pages 3-8, 10-11, 17-18, 21-22, 1984) is withdrawn in view of arguments

Response to Arguments

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6. The rejection of claim 14 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states that the "question of whether the practice of an invention would require undue experimentation is evaluated by analyzing the In re Wands factors, referred to but not analyzed in the rejection". The response then addresses the factors (see page 8 of response). In response to these arguments, while it may be true that the level of skill in the art is high, and it may be true that one would know what conservative amino acids to substitute, the predictability in the art of protein folding and substitution of large non-proteinaceous polymers into a protein structure is not predictable. As evidenced by Haber (Biochemistry 52:1099-1106, 1964) fully reduced antibodies that are carboxymethylated are completely inactive (see page 1103). Although later Haber discusses the that an active product is formed without the intrerchain disulfide bond (see page 1105), the claim recites that a cysteine is replaced and one cysteine is covalently linked to a non-proteinaceous polymer molecule. The claims are not commensurate in scope with the enablement provided.). In response to these arguments, the arguments are not commensurate in scope with the claims. The claims recite an antibody that has a nonproteinaceous polymer covalently linked to a cysteine residue in either the light chain or the heavy chain. Although Haber may state that a disulfide bond is not needed for association, the claims require adding a

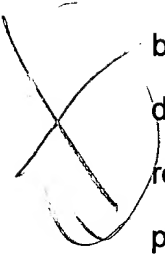
nonproteinaceous polymer to the antibody and Haber teach fully reduced and carboxymethylation of the antibody led to inactivity (see page 1103) and specific conformation of the H and L chains are necessary for binding antigen. Meaning that covalent modification by adding even a small chemical moiety such as carboxymethyl resulted in no activity. Thus, one skill in the art would reasonable conclude that adding a larger molecule such as a 20kD or larger PEG moiety would not allow the H and L chains to associate and to be active. There is no evidence in the specification or in the prior art of record to indicate that adding a nonproteinaceous polymer as large as 20Kd (or larger) to the cysteine in the H-L disulfide bond would result in a functioning antibody.

Thus, undue experimentation would be require to make and use the instantly claimed antibody fragments.

7. The rejection of claims 1-34 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-37 of copending Application No. 09/489,394 is maintained.

The response filed 10/3/01 has been carefully considured but is deemed not to be persuasive. The response states that upon entry of the present amendment the double patenting will be the only remaining rejections and accordingly the examiner is requested to withdraw both provisional obvious-type double patenting rejections in the parent case, allow the present case and repeat the double patenting rejection, if appropriate, in 09/489394 and 09/234182. in response to this argument no terminal disclaimer has been filed.

8. The rejection of claims 1, 10-12, and 14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 7, 19, 26-27 of copending Application No. 09/234,182 is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states that upon entry of the present amendment the double patenting will be the only remaining rejections and accordingly the examiner is requested to withdraw both provisional obvious-type double patenting rejections in the parent case, allow the present case and repeat the double patenting rejection, if appropriate, in 09/489394 and 09/234182. In response to this argument no terminal disclaimer has been filed.

9. The rejection of claims 1, 13, 18-22, and 29-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states "Faanes et al only exemplifies the PEGylation of full-length anti-ICAM antibody with 5 kD PEG" and later the response is directed to Faanes as not having an enabling disclosure for conjugates having an apparent size of at least about 500 kD (see page 10 of response and page 14 of response, fourth paragraph). In response to these arguments, it is noted that no scientific evidence is provided to indicate that that Faanes et al' conjugates would not work with higher molecular weight PEG, and in fact Faanes et al teaches conjugates with up to 40 kD (see column 12, lines 62-63).

10. The rejection of claims 1-13, 15-16, 18-24, 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states "Faanes et al only exemplifies the PEGylation of full-length anti-ICAM antibody with 5 kD PEG" and "Nor would a person skilled in the art have a reasonable expectation of success to use such conjugates for the purpose disclosed in the present application based on the Faanes et al disclosure alone, without the benefit of the disclosure of the present application" (see page 12 of response) and 'Faanes' objective by preparing their antibody conjugates is entirely different from the objective of the present inventors" (see page 14 of response). In response to these arguments, again it is noted that no scientific evidence is provided to indicate that that Faanes et al' conjugates would not work with higher molecular weight PEG, and in fact Faanes et al teaches conjugates with up to 40 kD (see column 12, lines 62-63).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that the instant application gives different reasons to prepare antibody conjugates, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The fact remains that it would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a conjugate consisting of PEG molecules attached to the antibody at various amounts with various molecular weight PEG molecules as taught by Faanes et al.

11. The rejection of claims 1-13, 15-25, 28-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) and further in view of Zapata et al (FASEB J. 9:A1476, 1995) is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states "applicants have discussed the deficiencies of the disclosure of Faanes et al " and "Zapata et al do not make up for the deficiencies" and "the 6-fold decrease in the serum clearance rate reported in Zapata et al for the 10 kD PEGylated Fab' would not lead the practitioner to predict a 180-fold decrease in serum clearance rate by the fab'-PEG(40 kD) conjugate of the present invention" (see page 13 of response). In response to these arguments, Zapata et al does teach a decrease in clearance with the 10 kD vs. the 5 kD PEG but does not state a numerical value, it is unclear where the numerical value (6-fold decrease) from the response is stated in Zapata et al. Therefore it is obvious in view of Zapata et al that higher MW PEG would lead to even a more pronounced effect than the 5 or 10 kD PEG.

12. The rejection of claims 1 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95) and further in view of Harlow et al (Antibodies A Laboratory Manual, Cold Spring Harbor Laboratories, pp 324-339, 1988) is maintained

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states "Harlow et al does not make up for the deficiencies of Faanes et al" (see page 14 of response). In response to this argument, the Faanes et al reference has been discussed and Harlow et al clearly teaches non-proteinaceous labels such as 125I, which would be obvious to conjugate to antibodies for detection.

13. The rejection of claims 1, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faanes et al as applied to claim 1 above and further in view of Doerschuk et al (WO 95/23865, 9/8/95) is maintained.

The response filed 10/3/01 has been carefully considered but is deemed not to be persuasive. The response states "Doerschuk has no teachings that would make up for this deficiency" of Faanes et al" (see page 14 of response). In response to this argument, the Faanes et al reference has been discussed and Doerschuk clearly teaches the IL-8 antibody which could obviously be used for conjugates of Faanes et al.

Conclusions

14. No Claims are allowed.

15. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Respectfully,

Larry R. Helms Ph.D.

703-306-5879


SHEELA HUFF
PRIMARY EXAMINER